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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,154	04/24/2002	George N. Cox III	4152-3-PUS	6320

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EXAMINER	
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1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,154	COX ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *Claims 67-68, 77-78, 80-87, 89-94, 96, 102, 104-105, 125-138* is/are pending in the application.

4a) Of the above claim(s) *87 and 89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67,68,77,78,80-86,90-94,96,102,104,105 and 125-137* is/are rejected.

7)☒ Claim(s) *138* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application, Amendments, And/Or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

The Declaration under 37 CFR 1.131 of Drs. George Cox and Daniel Doherty submitted on 20 August 2007 is acknowledged. Applicant's amendment of the claims filed 20 August 2007 has been entered.

Claims 1-66, 69-76, 79, 88, 95, 97-101, 103, 106-124 have been cancelled. New claims 125-138 have been added. Claims 67-68, 77-78, 80-87, 89-94, 96, 102, 104-105, 125-138 are pending. Claims 87, 89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 67-68, 77-78, 80-86, 90-94, 96, 102, 104-105, 125-138 are under examination.

Claim Objections/Rejections Withdrawn

The objection to claims 79, 103, 116 and 122 for reciting non-elected species is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 70 and 96 under 35 U.S.C. 112, second paragraph, as being indefinite for reciting an EC_{50} value without defining what assay system to use to determine the EC_{50} value, is withdrawn in response to Applicant's cancellation and amendment of the claims to limit "using a human UT7/epo cell line that proliferates in response to EPO".

The rejection of claim 105 under 35 U.S.C. 112, second paragraph, as being indefinite for reciting "dimeric fusion protein", which lacks antecedent basis, is withdrawn in response to Applicant's amendment of the claim.

The rejection of claims 67-70 and 77-84 under 35 U.S.C. 102(a) as being anticipated by Sytkowski et al. (WO 99/02709), is withdrawn in response to Applicant's submission of the Declaration under 37 CFR 1.131 of Drs. George Cox and Daniel Doherty to show evidence that the instant application was reduced to practice prior to the publication date of January 21, 1999 of WO 99/02709 by Sytkowski.

The rejection of claims 106, 109, 110, 112, 113 and 116 under 35 U.S.C. 102(e) as being anticipated by Sytkowski et al. (U. S. Patent NO: 6,242,570), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 90-96 and 102-104 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), in view of Mapelli et al. (U.S. Patent 5,519,115), is withdrawn in response to Applicant's submission of the Declaration under 37 CFR 1.131 of Drs. George Cox and Daniel Doherty to antedate the reference as described above.

The rejection of claims 114, 115, 117, 118, and 122-124 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (U. S. Patent NO: 6,242,570), in view of Mapelli et al. (U.S. Patent 5,519,115), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 85 and 86 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), in view of Strom et al. (WO 99/02711), is withdrawn in response to Applicant's submission of the Declaration under 37 CFR 1.131 of Drs. George Cox and Daniel Doherty to antedate the reference as described above.

New Grounds of Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 67-68, 77, 80-84, 126-129, 137 are rejected under 35 U.S.C. 102(e) as being anticipated by Lauffer et al. (US 2001/0053539, which has a priority date on 28 June 1990).

The claims are drawn to a fusion protein, a pharmaceutical composition thereof, a nucleic acid encoding same, a mammalian host cell transformed with the nucleic acid, and method of expressing and purifying same, wherein the fusion protein comprises an

erythropoietin joined without an intervening peptide to an Ig domain that does not contain a variable region (claim 67, 77, 80-84, 126, 137); wherein the Ig domain is selected from the group consisting of IgG-Fc, IgG-C_H and IgG-C_L (claim 68); wherein the EPO is a full length human EPO (claim 127); wherein the fusion protein has the recited EC_{50} (claims 126, 128-129, 137).

Lauffer et al. teach a human erythropoietin (EPO) fusion protein conjugated to various portions of the constant regions of heavy or light chains of immunoglobulin of various subclasses (IgG, IgM, IgA, IgE), preferably, the constant part of the heavy chain of human IgG1, where fusion takes place at the hinge region [0006]. Lauffer et al. teach an example of such huEPO-Ig fusion, in which the codon for the penultimate C-terminal amino acid residue of the EPO (Asp) is present in a BamH1 recognition sequence, and the reading frame in the BamH1 site is such that ligation with the BamH1 site in the pCD4Eγ1 results in a gene fusion with a reading frame continuous from the initiation codon of EPO cDNA to the stop codon of the heavy chain of IgG1 [0041-0042] (claims 67-68, 126-127, 137). Lauffer et al. teach a nucleic acid and a vector encoding the fusion protein [0042] (claim 80), a mammalian host cell expressing the fusion protein, and a method for expressing and further purifying the fusion protein by affinity chromatography (see Lauffer et al. claim 20) (claims 81-84). Lauffer et al. teach that the EPO-Ig fusion is particularly advantageous because it provides the straightforward purification and improves pharmacokinetic properties (claim 77).

The huEPO-Ig fusions taught by Lauffer et al. meet the limitation of "without an intervening peptide linker", because the claims do not define the sequences for the

erythropoietin and the Ig domain. The specification defines EPO as encompassing active variants of the protein (variants of EPO of any species, e.g., human, murine, chicken etc.); the term "active variants" means a fragment of a soluble protein that substantially retains the biological activity of the full-length protein (pp. 7, lines 24-26). The specification defines that "the Ig domain includes the constant region such as, for example, an IgG-Fc, IgG-C_H, an Fc or C_H domain from another Ig class, i.e., IgM, IgA, IgE, IgD or a light chain constant domain; truncations and amino acid variants or substitutions of these domain also are included" (pp. 7, lines 35-38). Therefore, even though there are amino acid residues that are not normally present in the natural human erythropoietin and natural human IgG1 present at the junction of the EPO-Ig of Lauffer et al., they can be considered as a variant of the EPO or Ig-C.

While Lauffer et al. do not expressly teach an EC_{50} value as recited in the claims for the fusion protein (claims 126, 128-129, 137), this activity is inherent to the protein since it has exactly the structure and pharmaceutical properties recited in the claims. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 90-94, 96, 104, 130-136 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Lauffer et al. (US 2001/0053539), in view of Mapelli et al. (U.S. Patent 5,519,115, issued on 21 May 1996).

Lauffer et al. teach as set forth above. Lauffer et al., however, do not teach conjugating an erythropoietin and an Ig domain with a peptide linker that consists of between 2 and 7 amino acid residues, or consists of a mixture of 2, 4, or 7 amino acid residues, selected from the group consisting of glycine and serine (claims 90, 92, 131-132); wherein the petide linker is SerGly, or SEQ ID NO: 1 (claims 93, 94).

Mapelli et al. teach the use of a small bridge, e.g., small bridges of 5 amino acids or less, in the construction of oligopeptides (column 24, lines 21-24). Mapelli et al. teach that these small bridges prevent disadvantageous steric hindrance between discrete monomers, and provide a sufficient degree of flexibility to the oligopeptide to allow for the formation of advantageous conformations (column 24, lines 7-20). Mapelli et al. teach that undesirable peptide secondary structures such as alpha helix or beta strands which may dominate the structure of the resulting oligomer and hinder potential interactions between the monomers generally require more than five amino acids in length (column 24, lines 29-34). Mapelli et al. teach that Gly side chain moieties are unlikely to sterically hinder any potential folding of the oligomer, and cannot participate in energenically stable bond structure (column 24, lines 53-63). Mapelli et al. further give several example of such Gly-rich linkers, e.g., bridges having 2 and 4 amino acids, Ser-Gly-Gly-Ser (identical to SEQ ID NO: 1) (column 25, line 6), Ser-Gly (column 27, line 23).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the teachings of Lauffer et al., with those of Mapelli et al., to use small Gly-rich linkers, such as Ser-Gly-Gly-Ser (SEQ ID NO: 1) or Ser-Gly, to link erythropoietin and Ig domain. One of ordinary skill in the art would have been motivated to combine the teachings, because Lauffer et al. teach that conjugating erythropoietin with IgG-C_H can improve pharmacokinetic properties, and Mapelli et al. teach that small bridges of 5 amino acids or less, such as SerGly or Ser-Gly-Gly-Ser, are particularly useful in the construction of oligopeptides because they prevent disadvantageous steric hindrance and provide a sufficient degree of flexibility to the oligopeptide to allow for the formation of advantageous conformations. Therefore, the combined teachings provide a reasonable expectation of successfully linking the two polypeptide components without affecting the structure and biological activity of the resulting fusion protein.

Claims 133-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Lauffer et al. (US 2001/0053539), in view of Mapelli et al. (U.S. Patent 5,519,115), and further in view of Qiu et al. (J. Biol Chem., 1998, May 1,273(18):11173-11176).

Lauffer et al. and Mapelli et al. teach as set forth above. They, however, do not teach conjugating an erythropoietin and an Ig domain with a peptide linker that consists of 7 amino acid residues selected from the group consisting of glycine and serine (claims 133-135).

Qiu et al. teach the use of a sequence encoding 3 to 7 glycine residues for the construction of a dimeric EPO (pp. 11174, Fig 1). Qiu et al. teach that the polyglycine linker can confer a functional conformation for the EP dimmer molecule (pp. 11176, Fig. 6).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the teachings of Lauffer et al. and Mapelli et al., with those of Qiu et al., to use a polyglycine linker encoding 3 to 7 glycine residues to link erythropoietin and Ig domain. One of ordinary skill in the art would have been motivated to combine the teachings, because Lauffer et al. teach that conjugating erythropoietin with IgG-C_H can improve pharmacokinetic properties, Mapelli et al. teach that Gly side chain moieties are unlikely to sterically hinder any potential folding of the oligomer, and glycine-rich linkers are particularly useful in the construction of oligopeptides, and Qiu et al. teach that such polyglycine linkers consisting of 3-7 glycine residues that can confer a functional conformation for the EPO dimer molecule. Therefore, the combined teachings provide a reasonable expectation of successfully linking the two polypeptide components without affecting the structure and biological activity of the resulting fusion protein.

Claims 78, 86, 102 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Lauffer et al. (US 2001/0053539), in view of Sytkowski (U.S. Patent 5,580,853, issued on 3 December 1996).

Lauffer et al. teach as set forth above. Lauffer et al., however, do not teach a composition comprising a dimeric EPO-Ig fusion protein essentially free of monomeric fusion protein (claims 78, 102), nor teach purifying the dimeric fusion protein by using size-exclusion chromatography (claims 86, 105).

Sytkowski teaches that multimeric EPO comprising two or more EPO molecules covalently linked together by thioether bonds exhibit increased bioactivity (column 2, lines 44-48). Sytkowski teaches using HPLC to separate dimer/multimer EPO from the monomers (column 7, lines 44-49).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the teachings of Lauffer et al., with those of Sytkowski, to link two EPO-Ig molecules by thioether bonds. One of ordinary skill in the art would have been motivated to combine the teachings, because Lauffer et al. teach that conjugating erythropoietin with IgG-C_H can improve pharmacokinetic properties, and Sytkowski teaches that multimeric EPO comprising two or more EPO molecules exhibit increased bioactivity. Therefore, the combined teachings provide a reasonable expectation of successfully making a multimeric EPO molecule with an increased pharmacokinetic properties and bioactivity.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 125 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 125 recites "the natural erythropoietin amino acid sequence and the natural immunoglobulin domain amino acid sequenece". Without a SEQ ID or specifying the species where the sequence is generated, e.g., a human, a mouse, a canine or a bovine sequence, the metes and bounds cannot be determined.

Conclusion

Claim 138 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

NO CLAIM IS ALLOWABLE.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nicole, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
November 7, 2007

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